UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

March 14, 2006

MEMORANDUM

SUBJECT: Review of "Stroking Test in Dogs After Topical Application of Imidacloprid 10% (w/v) + Permethrin 50% (w/v) Spot-On"

FROM: Charles Smith, Environmental Scientist/Risk Assessor 3/23/06
Reregistration Branch 2
Health Effects Division (7509C)

THRU: Alan Nielsen, Branch Senior Scientist Alan Nielsen 3/23/06
Reregistration Branch 2
Health Effects Division (7509C)

TO: Jaqueline Guerry, Chemical Review Manager
Reregistration Branch 3
Special Review and Reregistration Division (7508C)

DP Barcode: 320041
PC Code: 109701
MRID Number: 465941-03

Attached is a review of the MRID 465941-03 "*Stroking Test in Dogs After Topical Application of Imidacloprid 10% (w/v) + Permethrin 50% (w/v) Spot-On*" submitted by Bayer Health Care LLC. The purpose of the study was to measure the dislodgeability of the test substance from the haircoats of dogs treated with a spot-on formulation containing imidacloprid and permethrin as the active ingredients.

The test substance was administered to Beagle dogs by topical application to the back (spine) using pipettes intended for commercial application. The test substance (2.5 ml) was applied in 4 single spots. Residues were collected to assess the postapplication exposure from treated dogs by stroking the dogs three times from head to tail over the application spots, while wearing cotton gloves. Medium pressure was used to stroke the dogs. Samples were collected at each of the following sampling intervals: 30 minutes, 2 hours, 12 hours, and 24 hours after application. A separate glove was used for each of five animals tested. The animals were observed daily for general clinical signs.

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The study authors reported the amounts of imidacloprid and permethrin per glove for each animal in each group at each sampling period. Means, standard deviations, relative standard deviations, minimums and maximums were also reported. The results provided in the Study Report were verified and then the arithmetic and geometric means and standard deviation were calculated for the residues at each interval. When residues were less than the limit of quantitation (LOQ), ½ LOQ was used in the calculations. For imidacloprid, average residues were 0.543 ± 0.569 mg/glove at 30 minutes after treatment, less than the LOQ at 2 hours after treatment, 0.715 ± 0.375 mg/glove at 12 hours after treatment, and 1.14 ± 0.487 mg/glove at 24 hours after treatment. Imidacloprid residues were less than the LOQ in one of the five replicates at the 30 minute and 12 hour intervals and in three of the five replicates at the 2 hour interval. For permethrin, average residues were 2.71 ± 3.42 mg/glove at 30 minutes after treatment, less than the LOQ at 2 hours after treatment, 2.75 ± 1.26 mg/glove at 12 hours after treatment, and 3.29 ± 1.40 mg/glove at 24 hours after treatment. Permethrin residues were less than the LOQ in two of the five replicates at the 30 minute interval, four of the five replicates at the 2 hour interval, and in one of the five replicates at the 12 hour interval.

The primary review was conducted by Versar, Inc. A secondary review was conducted by HED. A study protocol was not provided with the study and no applicable guidelines specific to this type of study were available to assess the accuracy and validity of the methods utilized. However, OPPTS Series 875 Part B, Guideline 875.2400: Dermal Exposure, Postapplication and Part C Guidelines were used to review this study.

Based on the information presented in the study, the following issues of concern are noted:

- The post-application activity monitored in this study included stroking a dog only three times with the hand. A typical exposure event most likely involves more strokes with the hand and hugging the dog.
- The area of the dog stroked was down its spine, including directly over the application spot. The study, "Pharmacokinetics of the Compound Preparation Permethrin 50%/Imidacloprid 10% Spot On in the Hair" (MRID 465941-02), indicates that the test product disperses to the sides of the dogs. No information is known about how quickly the product disperses in the dog's coat.
- The individual residues were highly variable at each sampling interval, as indicated by large standard deviations.
- There were a large number of samples with residues below the LOQ. Imidacloprid residues were less than the LOQ in one of the five replicates at the 30 minute and 12 hours intervals and in three of the five replicates at the 2 hour interval. Permethrin residues were less than the LOQ in two of the five replicates at the 30 minute interval, four of the five replicates at the 2 hour interval, and in one of the five replicates at the 12 hour interval.
- Highly absorbent cotton gloves were used to the collect the samples. However, no absorbency data were presented to quantify the difference between cotton gloves and bare hands, and residues in many of the cotton glove samples were less than the LOQ.
- The study was conducted with only a single type of dog.
- The study did not provide the duration of the monitoring event; therefore, the data could not be normalized to time.

- The study did not provide the palmar surface area; therefore the data could not be adjusted for surface area.
- Field fortification samples were not collected.
- The storage conditions of the samples prior to receipt at the analytical laboratory were not provided. Additionally, information regarding the storage stability of the samples was not provided. The samples were analyzed within 35 days of collection.

Versar inc.

MEMORANDUM

TO:	Bill Smith	cc:	110082.5000.001.01 Chuck Peck
FROM:	Karie Riley/Kelly McAloon/Sally McDonald		
DATE:	September 12, 2005		
SUBJECT:	Review of "*Stroking Test in Dogs After Topical Application of Imidacloprid 10% (w/v) + Permethrin 50% (w/v) Spot-On*" (MRID 465941-03)		

This report reviews a study entitled "*Stroking Test in Dogs after Topical Application of Imidacloprid 10% (w/v) + Permethrin 50% (w/v) Spot-On*" (MRID 465941-03). There are no applicable OPPT Guidelines established for this type of study. However, OPPTS Series 875 Part B, Guideline 875.2400: Dermal Exposure, Postapplication and Part C Guidelines were used to review this study. General issues of concern were also noted with the review.

Reviewers: Karie Riley/Kelly McAloon/Sally McDonald **Date:** September 12, 2005

STUDY TYPE: Active Transfer; Animal Hair

TEST MATERIAL: The test substance was a spot-on formulation containing 10% (w/v) imidacloprid and 50% (w/v) permethrin as the active ingredients.

SYNONYMS: Imidacloprid: 1-((6-CHLORO-3-PYRIDINYL)METHYL)-N-NITRO-2-IMIDAZOLIDINIMINE

Permethrin: 3-(PHENOXYPHENYL) METHYL-3-(2,2-DICHLOROETHENYL)-2,2-DIMETHYL-CYCLOPROPANE-CARBOXYLATE

CITATION:

Author:	Dr Th. Bach and Dr. R. Krebber
Title:	*Stroking Test in Dogs after Topical Application of Imidacloprid 10% (w/v) + Permethrin 50% (w/v) Spot-On*
Study Completion Date:	December 6, 2002
Testing Facility:	Bayer Health Care AH-R&D Antibiotics Animal Center Bayer AG, 51368 Leverkusen Germany
Identifying Codes:	Project No. 1303; Study No. V 02-04; AHD Study No. 142957; Bayer Report No. 75755 MRID 465941-03

SPONSOR: Bayer Health Care LLC
Animal Health Division
P.O. Box 390
Shawnee Mission, KS 66201

EXECUTIVE SUMMARY:

This report reviews "*Stroking Test in Dogs After Topical Application of Imidacloprid 10% (w/v) + Permethrin 50% (w/v) Spot-On*" submitted by Bayer Health Care LLC. The purpose of the study was to measure the dislodgeability of the test substance from the haircoats of dogs treated with a spot-on formulation containing imidacloprid and permethrin as the active ingredients.

The test substance was administered to Beagle dogs by topical application to the back (spine) using pipettes intended for commercial application. The test substance (2.5 ml) was applied in 4 single spots. Residues were collected to assess the postapplication exposure from treated dogs by stroking the dogs three times from head to tail over the application spots, while wearing cotton gloves. Medium pressure was used to stroke the dogs. Samples were collected at each of the following sampling intervals: 30 minutes, 2 hours, 12 hours, and 24 hours after application. A separate glove was used for each of five animals tested. The animals were observed daily for general clinical signs.

The study authors reported the amounts of imidacloprid and permethrin per glove for each animal in each group at each sampling period. Means, standard deviations, relative standard deviations, minimums and maximums were also reported. Versar verified the results provided in the Study Report. Versar calculated the arithmetic and geometric means and standard deviation for the residues for each interval. When residues were less than the limit of quantitation (LOQ), Versar used ½ LOQ in the calculations. For imidacloprid, average residues were 0.543 ± 0.569 mg/glove at 30 minutes after treatment, less than the LOQ at 2 hours after treatment, 0.715 ± 0.375 mg/glove at 12 hours after treatment, and 1.14 ± 0.487 mg/glove at 24 hours after treatment. Imidacloprid residues were less than

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the LOQ in one of the five replicates at the 30 minute and 12 hour intervals and in three of the five replicates at the 2 hour interval. For permethrin, average residues were 2.71 ± 3.42 mg/glove at 30 minutes after treatment, less than the LOQ at 2 hours after treatment, 2.75 ± 1.26 mg/glove at 12 hours after treatment, and 3.29 ± 1.40 mg/glove at 24 hours after treatment. Permethrin residues were less than the LOQ in two of the five replicates at the 30 minute interval, four of the five replicates at the 2 hour interval, and in one of the five replicates at the 12 hour interval.

Versar also calculated residues in terms of the amount of active ingredient applied. For imidacloprid, average residues were 985 ± 1033 mg/lb ai applied at 30 minutes after treatment, less than the LOQ at 2 hours after treatment, 1297 ± 680 mg/lb ai applied at 12 hours after treatment, and 2065 ± 884 mg/lb ai applied at 24 hours after treatment. For permethrin, average residues were 983 ± 1242 mg/lb ai applied at 30 minutes after treatment, less than the LOQ at 2 hours after treatment, 998 ± 459 mg/lb ai applied at 12 hours after treatment, and 1195 ± 508 mg/lb ai applied at 24 hours after treatment.

For both imidacloprid and permethrin, the average residues detected on the gloves decreased to levels below the LOQ from the 30-minute sampling interval to the 2-hour sampling interval, and then increased to the highest concentration at the 24-hour sampling interval.

A study protocol was not provided with the study and no applicable guidelines specific to this type of study were available to assess the accuracy and validity of the methods utilized. However, OPPTS Series 875 Part B, Guideline 875.2400: Dermal Exposure, Postapplication and Part C Guidelines were used to review this study.

Based on the information presented in the study, the following issues of concern are noted:

- The post-application activity monitored in this study included stroking a dog only three times with the hand. A typical exposure event most likely involves more strokes with the hand and hugging the dog.
- The area of the dog stroked was down its spine, including directly over the application spot. The study, "Pharmacokinetics of the Compound Preparation Permethrin 50%/Imidacloprid 10% Spot On in the Hair" (MRID 465941-02), indicates that the test product disperses to the sides of the dogs. No information is known about how quickly the product disperses in the dog's coat.
- The individual residues were highly variable at each sampling interval, as indicated by large standard deviations.
- There were a large number of samples with residues below the LOQ. Imidacloprid residues were less than the LOQ in one of the five replicates at the 30 minute and 12 hours intervals and in three of the five replicates at the 2 hour interval. Permethrin residues were less than the LOQ in two of the five replicates at the 30 minute interval, four of the five replicates at the 2 hour interval, and in one of the five replicates at the 12 hour interval.
- Highly absorbent cotton gloves were used to the collect the samples. However, no absorbency data were presented to quantify the difference between cotton gloves and bare hands, and residues in many of the cotton glove samples were less than the LOQ.
- The study was conducted with only a single type of dog.
- The study did not provide the duration of the monitoring event; therefore, the data could not be normalized to time.
- The study did not provide the palmar surface area; therefore the data could not be adjusted for surface area.
- Field fortification samples were not collected.
- Detailed information regarding the analytical methodology for imidacloprid was not provided.

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- The complete method validation results for imidacloprid may not have been provided (see next bullet for explanation).

- Versar could not distinguish between the method validation recoveries conducted prior to the start of the analysis and the concurrent recoveries conducted during analysis. Method validation and concurrent recovery results were reported in the same table of the Study Report.

- The storage conditions of the samples prior to receipt at the analytical laboratory were not provided. Additionally, information regarding the storage stability of the samples was not provided. The samples were analyzed within 35 days of collection.

- The application rate was not specified on the product label; however, according to "Assessment of Residential Exposure to Permethrin during and following Spot-on Application of K9 Advantix™ to Dogs" (MRID 46594 1-01), the amount which can be applied to a large dog is 4 ml. In this study, 2.5 ml was applied to dogs weighing between 24 and 35 lbs.

COMPLIANCE:
Signed and dated GLP, Data Confidentiality, and Quality Assurance statements were provided. The study sponsor waived claims of confidentiality within the scope of FIFRA Section 10(d)(1)(A), (B), or (C). The Study Report indicated that the study was not necessarily conducted according to the requirements of EPA Good Laboratory Practice Standards (40 CFR Part 160), but was conducted according to OECD Principles of Good Laboratory Practices.

GUIDELINE OR PROTOCOL FOLLOWED: A study protocol was not provided with the Study Report. OPPTS Series 875 Part B, Guideline 875.2400: Dermal Exposure, Postapplication and Part C Guidelines were used to review this study.

I. MATERIALS AND METHODS

A. Materials:

1. Test Material:

Formulation:	A spot-on formulation containing a nominal 10% (w/v) imidacloprid and 50% (w/v) permethrin
Lot/Batch # formulation:	KP005WU (pipette) and 2224EA (article)
Formulation guarantee:	According to the certificate of analysis, the product contains 9.9 g imidacloprid/100 ml and 50.8 g permethrin /100 ml.
Purity:	The reference substances had purities of 99.7% for imidacloprid, 96.1% for permethrin, 98.2% for chloroacetylenic permethrin (internal standard), and 10 mg/ml in acetonitrile for imidacloprid-pyridine-5-d-methylene-d2, 13C (internal standard)
CAS #(s):	Imidacloprid: 105827-78-9 Permethrin: 52645-53-1

2. Relevance of Test Material to Proposed Formulation(s):

The test substance is a solution of imidacloprid and permethrin designed for spot-on application animals, which is the same as the product K9 Advantix™ (the product name was obtained from "Assessment of Residential Exposure to Permethrin during and following Spot-on Application of K9 Advantix™ to Dogs", MRID 465941-01).

B. Study Design:

1. Test Animal/Site Description:

Number and Type of Animals:	Twenty adult beagle dogs (18 male and 2 female) from Bayer AG, 51368 Leverkusen Germany dog colony were used in this study. These dogs were bred and reared at Harlan Winkelmann Germany and Marshall Farms USA. The dogs were identified through ear tattooing.
Weight of Animals:	The dogs weighed between 11 and 16 kg (24 and 35 lbs).
Animal Assignment:	Five dogs were randomly assigned to each of four treatment groups.
Housing:	Testing was conducted at Bayer Health Care facilities. The room used for the test was separated from the other rooms at the facility. The dogs were kept in individual pens measuring about 1.8 m^2. Contact between the dogs was prevented. The boxes were cleaned once a day. Housing and husbandry were in compliance with the National Code for Animal Protection issued May 1998.
Environmental Conditions:	Room temperature and relative humidity were measured by thermohygrograph over 4 days. The temperature was 5°C and the humidity ranged from 55 to 75%, except during the daily cleaning sessions in which the humidity reached 90%. Artificial lighting was provided for 12 hours from 6 am to 6 pm. Test animals were acclimatized for a few days prior to the start.
Feeding:	Dogs were fed a commercially available dog food (ssniff dog extrudiert Alleinfutter für Hunde) according to the manufacture's directions. Feeding was after termination of sampling on days -1, 0 and 1. Tap water was provided *ad libitum*.
Animal Health:	Animals used in the study had to be regularly vaccinated and should not have received any pre- medications within the last 3 months prior to the start of the study that might interfere with the study objectives.
Clinical Observations:	Special clinical observations were performed on days -1, 0 and 1 after treatment. Each animal was examined concerning hair and skin coat, gingivae, respiratory tract, cardiovascular system, digestive tract, urinary and reproductive system, musculoskeletal system and central nervous system.

2. Surface(s) Monitored:

Types of Surface(s):	Dog haircoats
Areas treated:	Dogs were treated with the test formulation by administering the formulation to the skin on the back.
Other products used:	No

3. Physical State of Formulation as Applied : Liquid (spot-on formulation)

4. Application Rates and Regimes:

Application Equipment:	The test material was applied with pipettes intended for commercial use of the product.
Application Regime:	On day 0, each animal was treated once in their pen. The total dose was applied in 4 spots on the skin of the back by parting the hair.
Application rate(s):	Each dog received a dose of 2.5 ml product, which equates to 0.25 g imidacloprid and 1.25 g permethrin. An application rate was not specified on the product labels; however, according to MRID 465941-01 ("Assessment of Residential Exposure to Permethrin during and following Spot-on Application of K9 Advantix™ to Dogs"), the amount, which can be applied to a large dog is 4 ml.

C. Sampling:

Surface Areas Sampled:	The surface area of neither the stroking area nor the palmar surface area were provided.
Sampling Time:	The exact length of time to complete a single stroke or the entire stroking procedure was not provided. However, the sample collection times indicate that it took less than 5 minutes per dog to collect a sample.
Number of sampling intervals:	There were four sampling intervals after application, including thirty minutes after application (test group 1), 2 hours after application (test group 2), 12 hours after application (test group 3), and 24 hours after application (test group 4). However, another study (MRID 465941-02 "Pharmacokinetics of the Compound Preparation Permethrin 50%/Imidacloprid 10% Spot On in the Hair") determined peak residues over time in samples of dog hair from dogs, which had been treated with the same spot-on formulation as used in this study. In this earlier study, the application was made to the back of the dogs, but the hair samples were collected on the sides of the dogs. Peak residues in dog hair were found on day 4 after treatment. This current study only collects data from the first 24 hours following treatment.
Replicates per sampling interval:	Five dogs (one test group) were sampled at each interval.
Method and Equipment:	The sampling was conducted by stroking the dogs with an adult hand covered with a dry, bleached highly absorbent cotton glove. Disposable nitrile gloves were worn under the cotton gloves to avoid any cross contamination.
Sampling Procedure:	The dogs stood on the floor while one person kept the dog in position and the other person took the sample. The sample was collected by stroking the fur with medium uniform pressure three times from head to tail at the application spot. The same person took all samples.

D. Sample Handling and Storage:
The samples were delivered to the laboratory on May 17, 2002 and stored frozen at -18°C or below until analysis.

II. ANALYTICAL METHODOLOGIES

A. Extraction method: The residues of imidacloprid and permethrin were extracted by shaking with acetonitrile and subsequent treatment in an ultrasonic bath.

B. Detection methods: Imidacloprid residues were determined according to the method 00431/M005 (MR-168/02) without further purification of the extract by HPLC with detection by tandem mass spectrometry. An internal standard was used.

Permethrin residues were determined according to the method 00431/M006 (MR-169/02) without further purification of the extract by gas chromatography with mass spectrometric detection. An internal standard was used. Typical operating conditions for the permethrin determination were provided in a separate document ("Method for GC-MS Determination of Permethrin on Cotton Gloves", MRID 465941-04) and are shown in Table 1.

Table 1: Typical Operating Conditions of GC/MS for Permethrin Determination

Injector	Cold on column
Injection Program	Modus: Splitless Splitless Time: 1 min Purge time: 0.7 min Initial Temp: 50°C Initial Time: 0.1 min Heating Rate: 12 °C/s Final Temp: 350 °C Final Time: 3 min
Injection volume	3 μL
Carrier Gas	Helium
Carrier Gas Pressure	74 kPa (100°C)
Operating Mode	Constant Flow
Detection	Selected Ion Monitoring
Target Ions	m/z = 163 and 183
Dwell Time	40 msec per target ion
Transfer Line	Capillary direct interface at 280°C
Ion Source	Electron Impact (70eV)
Column	Ultra 1, 25 m, ID 0.2 mm, film thickness 0.1 μm
Oven Program	100 °C (1 min) 50 °C/min 240 °C (1 min) 10 °C/min 280 °C (2 min)
Retention Times	Permethrin: approximately 7.9 and 8.0 minutes Internal Standard: 7.1 minutes

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Total Run Time	10.8 min

C. Method Validation:

Method 00431/M006A for permethrin was validated on cotton gloves. The results were reported in MRID 46594104 ("Method for GC-MS Determination of Permethrin on Cotton Gloves"). In the validation study, samples were fortified at 1.25, 2.5, 10 and 20 mg/glove. Individual recoveries ranged from 84 to 120%. The overall average recovery was 94% with a relative standard deviation of 9.5%. The recoveries are shown in Table 2. The recoveries at the low and high fortification levels (1.25 and 20 mg/glove) were also reported in the Study Report as recoveries from samples analyzed at the beginning of the analytical study (method validation recoveries) and during the analytical study (concurrent recoveries). It is unclear as to when the samples for the recoveries shown in Table 2 were fortified and analyzed. The limit of quantitation was reported as 1.25 mg for each glove.

A method validation study for imidacloprid was not provided. Table 3 identifies the recovery rates from method validation samples fortified and analyzed prior to the start of the analytical study and concurrent samples fortified and analyzed during the analytical study provided in the Study Report. It is unclear as to which samples were analyzed prior to or during the study. Individual recoveries ranged from 79 to 90%. The overall average recovery was 86%, with a relative standard deviation of 4.3%. The limit of quantitation was reported as 0.25 mg per glove.

Table 2. Method Validation/Concurrent Recovery Results for Permethrin

Fortification Level (mg permethrin/glove)	Recovery values (%)	Average Recovery (%)	Relative Standard Deviation (%)
1.25	94, 84, 93, 99, 93	93	5.8
2.5	90, 88, 88	89	1.3
10	92,86, 85	88	4.3
20	102, 120, 98, 89, 101	102	11.1
Overall		94	9.5

Table 3. Method Validation/Concurrent Recovery Results for Imidacloprid

Fortification Level (mg imidacloprid/glove)	Recovery values (%)	Average Recovery (%)	Relative Standard Deviation (%)
0.25	87, 88, 88, 85, 87	87	1.4
10	79, 88, 90, 80, 89	85	6.2
Overall		86.1	4.3

Instrument performance and calibration:

The measured concentration is calculated by reference of the sample response to a standard calibration line. Information regarding instrument performance and calibration were not provided.

E. Quality Control:

Lab Recovery:	According to the Study Report, for verification of the analytical method, "a validation was carried out at the beginning of the analytical part and concurrent recoveries during analyses were conducted" (page 22 of Study Report). The recoveries reported in the Study Report and in the permethrin method validation report (MRID 465941-04) are shown above in Tables 2 and 3.
Field Fortification:	Field fortification recoveries were not conducted as a part of this study.
Control Samples:	According to the Study Report, residues of imidacloprid or permethrin were not found above the LOQ in any of the control samples.
Storage Stability:	Information regarding storage stability of the samples was not provided. Based on sample collection dates and the analytical phase ending date, the samples were stored for no more than 35 days after collection.

III. RESULTS

A. Observations:

On the day prior to treatment, no abnormal clinical signs were found. Some of the dogs panted, therefore, a respiratory rate could not be taken in these dogs. No signs of disease were observed in any of the dogs post application on day 0 or day 1.

B. Glove Residues:

The study authors reported the amounts of imidacloprid and permethrin per glove for each animal in each group at each sampling period. Means, standard deviations, relative standard deviations, minimums and maximums were also reported. Versar verified the results provided in the Study Report.

Versar calculated the arithmetic and geometric mean residues as well as standard deviations for each interval, as shown in Table 4. When residues were less than the limit of quantitation (LOQ), Versar used ½ LOQ in the calculations. For imidacloprid, average residues were 0.543 ± 0.569 mg/glove at 30 minutes after treatment, less than the LOQ at 2 hours after treatment, 0.715 ± 0.375 mg/glove at 12 hours after treatment, and 1.14 ± 0.487 mg/glove at 24 hours after treatment. For permethrin, average residues were 2.71 ± 3.42 mg/glove at 30 minutes after treatment, less than the LOQ at 2 hours after treatment, 2.75 mg/glove ± 1.26 at 12 hours after treatment, and 3.29 ± 1.40 mg/glove at 24 hours after treatment.

Versar also calculated residues in terms of the amount of active ingredient applied. For imidacloprid, average residues were 985 ± 1033 mg/lb ai applied at 30 minutes after treatment, less than the LOQ at 2 hours after treatment, 1297 ± 680 mg/lb ai applied at 12 hours after treatment, and 2065 ± 884 mg/lb ai applied at 24 hours after treatment. For permethrin, average residues were 983 ± 1242 mg/lb ai applied at 30 minutes after treatment, less than the LOQ at 2 hours after treatment, 998 ± 459 mg/lb ai applied at 12 hours after treatment, and 1195 ± 508 mg/lb ai applied at 24 hours after treatment.

For both imidacloprid and permethrin, the average residues detected on the gloves decreased to levels below the LOQ from the 30-minute sampling interval to the 2-hour sampling interval, and then increased to the highest concentration at the 24-hour sampling interval.

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Table 4. Imidacloprid and Permethrin Residues from Gloves after Stroking Treated Dogs

Replicate No.	Imidacloprid[a] (mg/glove)	Permethrin[b] (mg/glove)	lb imidacloprid applied[c]	lb permethrin applied[c]	Imidacloprid (mg/lb ai applied)	Permethrin (mg/lb ai applied)
Group 1: 30 minutes after treatment						
1	0.4	1.68	0.000551	0.00276	726	610
2	0.4	1.87			726	679
3	0.25	<LOQ			454	<LOQ
4	<LOQ	<LOQ			<LOQ	<LOQ
5	1.54	8.74			2794	3172
Average	0.543	2.71			985	983
Geometric Mean	0.378	1.61			686	583
Standard Deviation	0.569	3.42			1033	1242
Relative Standard Deviation (%)	105	126			105	126
Group 2: 2 hours after treatment						
1	<LOQ	<LOQ	0.000551	0.00276	<LOQ	<LOQ
2	0.25	<LOQ			454	<LOQ
3	0.44	2.04			798	740
4	<LOQ	<LOQ			<LOQ	<LOQ
5	<LOQ	<LOQ			<LOQ	<LOQ
Average	0.213 (<LOQ)	0.908 (<LOQ)			386 (<LOQ)	329 (<LOQ)
Geometric Mean	0.185 (<LOQ)	0.792 (<LOQ)			335 (<LOQ)	287 (<LOQ)
Standard Deviation	0.138	0 633			250	230
Relative Standard Deviation (%)	64.8	69.7			65	70
Group 3: 12 hours after treatment						
1	<LOQ	<LOQ	0.000551	0.00276	<LOQ	<LOQ
2	1	4.01			1814	1455
3	0.82	2.93			1488	1063
4	0.59	2.98			1070	1081
5	1.04	3.21			1887	1165
Average	0.715	2.75			1297	998

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Table 4. Imidacloprid and Permethrin Residues from Gloves after Stroking Treated Dogs						
Replicate No.	Imidacloprid[a] (mg/glove)	Permethrin[b] (mg/glove)	lb imidacloprid applied[c]	lb permethrin applied[c]	Imidacloprid (mg/lb ai applied)	Permethrin (mg/lb ai applied)
Geometric Mean	0.575	2.34			1043	849
Standard Deviation	0.375	1.26			680	459
Relative Standard Deviation (%)	52.4	46.0			52	46
Group 4: 24 hours after treatment						
1	1.84	4.78	0.000551	0.00276	3338	1735
2	1.37	3.69			2486	1339
3	1.1	4.35			1996	1579
4	0.71	1.96			1288	711
5	0.67	1.69			1216	613
Average	1.14	3.29			2065	1195
Geometric Mean	1.06	3.03			1918	1098
Standard Deviation	0.487	1.40			884	508
Relative Standard Deviation (%)	42.8	42.5			43	42

a. Imidacloprid LOQ = 0.25 mg/glove. Average and standard deviation calculated using ½ LOQ.
b. Permethrin LOQ = 1.25 mg/glove. Average and standard deviation calculated using ½ LOQ.
c. 2.5 ml product/dog, which is equivalent to 1.25 g permethrin/dog and 0.25 g imidacloprid/dog.
Note: The data for each chemical were tested for normality using Shapiro-Wilks Test. The following results were obtained (it should be noted that due to the low sample size of each data set, the power of the test to determine normality decreases): imidacloprid: normal; permethrin: not normal

VI. CONCLUSION

In this study, the test substance was administered to beagle dogs by topical application to the back using pipettes intended for commercial application. Residues were collected to assess the postapplication exposure from treated dogs by stroking the dogs three times from head to tail, over the application spot. Using cotton gloves, samples were collected 30 minutes, 2 hours, 12 hours, and 24 hours after application. For both imidacloprid and permethrin, the average residues detected on the gloves decreased to less than the LOQ from the 30-minute sampling interval to the 2 hour sampling interval, and then increased to the highest concentration by the 24-hour sampling interval. Limitations and issues of concern with the study are provided below.

LIMITATIONS OF THE STUDY:

A study protocol was not provided with the study and no applicable guidelines specific to this type of study were available to assess the accuracy and validity of the methods utilized. However, OPPTS Series 875 Part B, Guideline 875.2400: Dermal Exposure, Postapplication and Part C Guidelines were used to review this study.

Based on the information presented in the study, the following issues of concern are noted:

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- The post-application activity monitored in this study included stroking a dog only three times with the hand. A typical exposure event most likely involves more strokes with the hand and hugging the dog.

- The area of the dog stroked was down its spine, including directly over the application spot. The study, "Pharmacokinetics of the Compound Preparation Permethrin 50%/Imidacloprid 10% Spot On in the Hair" (MRID 465941-02), indicates that the test product disperses to the sides of the dogs. No information is known about how quickly the product disperses in the dog's coat.

- The individual residues were highly variable at each sampling interval, as indicated by large standard deviations.

- There were a large number of samples with residues below the LOQ. Imidacloprid residues were less than the LOQ in one of the five replicates at the 30 minute and 12 hours intervals and in three of the five replicates at the 2 hour interval. Permethrin residues were less than the LOQ in two of the five replicates at the 30 minute interval, four of the five replicates at the 2 hour interval, and in one of the five replicates at the 12 hour interval.

- Highly absorbent cotton gloves were used to the collect the samples. However, no absorbency data were presented to quantify the difference between cotton gloves and bare hands, and residues in many of the cotton glove samples were less than the LOQ.

- The study was conducted with only a single type of dog.

- The study did not provide the duration of the monitoring event; therefore, the data could not be normalized to time.

- The study did not provide the palmar surface area; therefore the data could not be adjusted for surface area.

- Field fortification samples were not collected.

- Detailed information regarding the analytical methodology for imidacloprid was not provided.

- The complete method validation results for imidacloprid may not have been provided (see next bullet for explanation).

- Versar could not distinguish between the method validation recoveries conducted prior to the start of the analysis and the concurrent recoveries conducted during analysis. Method validation and concurrent recovery results were reported in the same table of the Study Report.

- The storage conditions of the samples prior to receipt at the analytical laboratory were not provided. Additionally, information regarding the storage stability of the samples was not provided. The samples were analyzed within 35 days of collection.

- The application rate was not specified on the product label; however, according to "Assessment of Residential Exposure to Permethrin during and following Spot-on Application of K9 Advantix™ to Dogs" (MRID 46594 - 01), the amount which can be applied to a large dog is 4 ml. In this study, 2.5 ml was applied to dogs weighing between 24 and 35 lbs.

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Name:
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APPENDIX A

Compliance Checklist for "*Stroking Test in Dogs After Topical Application Imidacloprid 10% (w/v) + Permethrin 50% (w/v) Spot-On*"

DRAFT
COMPLIANCE CHECKLIST
GUIDELINE 875.2400
DERMAL EXPOSURE MONITORING
POSTAPPLICATION

1. *The test substance must be the typical end use product of the active ingredient.* This criterion was met.

2. *The production of metabolites, breakdown products, or the presence of contaminants of potential toxicologic concern, should be considered on a case-by-case basis.* It is unclear if this criterion was met. There was no mention of metabolites, breakdown products or other contaminants.

3. *Applications should occur at the time of season that the end-use product is normally applied to achieve intended pest control.* This criterion does not apply to this study.

4. *Initiating testing immediately before a precipitation event should be avoided.* This criterion does not apply to this study.

5. *The end use product should be applied by the application method recommended for the crop. Information that verifies that the application equipment (e.g., sprayer) was properly calibrated should be included.* This criterion does not apply to this study.

6. *The application rate used in the study should be provided and should be the maximum rate specified on the label. However, monitoring following application at a typical application rate is more appropriate in certain cases.* The application rate (volume of product) was not specified on the product label; however, according to MRID 465941-01, the amount which can be applied to a large dog is 4 ml. In this study, 2.5 ml was applied to dogs weighing between 24 and 35 lbs.

7. *If multiple applications are made, the minimum allowable interval between applications should be used.* This criterion does not apply to this study. The test material was only applied once.

8. *A sufficient number of replicates should be generated to address the exposure issues associated with each population of interest. In general, the study should include minimum of 15 replicates per activity, distributed as follows: 5 replicates (i.e., individuals) on each of 3 monitoring periods (i.e., "n" days after application).* This criterion was met. There were five replicates at each of four monitoring periods.

9. *The monitoring period should be of sufficient duration to result in reasonable detectability on dosimeters. Monitoring should be conducted before residues have dissipated beyond the limit of quantification. Baseline samples should be collected before the exposure activity commences.* These criteria were partially met. Background samples were collected from each dog prior to application and analyzed. These residues were <LOQ. Residues from samples collected after application of the test substance were above the LOQ in only 65% of the samples (5 of the 20 imidacloprid samples and 7 of the 20 permethrin samples). The monitoring duration consisted of the time needed for three strokes of each dog. More strokes per replicate may have resulted in more samples with residues above the LOQ.

10. *Activities monitored must be clearly defined and representative of typical practice.* This criterion was partially met. The activity of stroking a dog is a typical post-application activity; however, only three strokes per replicate were conducted in this study. Additionally, postapplication activity also typically includes hugging. It should be noted that in this study, the stroking only took place at the application spot. Stroking will also likely occur on the sides of the dogs.

11. *Passive dosimetry studies must be carried out concurrently with transferable residue studies.* This criterion does not apply to this study.

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12. *The selected sites and seasonal timing of monitoring must be appropriate to the activity.* This criterion does not apply to this study.

13. *Studies should be conducted under different geographic/climatologic sites.* This criterion does not apply to this study.

14. *The sampling techniques (e.g., patches, whole-body dosimeters, hand rinse, gloves, fluorescent tracer) should be appropriate to the activities being monitored. The construction materials and location (i.e., inside or outside clothing) of monitoring devices and numbers (e.g., patches) should be appropriate to the use scenario. Hand rinse solutions must be appropriate to the pesticide being evaluated (i.e., selection of aqueous surfactants vs. isopropanol or other solutions, based on the physical chemical properties of the pesticide being evaluated.* This criterion was met. Transferable residue samples were collected from the dogs using highly absorbent cotton gloves. It should be noted that cotton gloves may absorb more of the active ingredients than bare human skin. No data were presented, however, to quantify the differences.

15. *Sufficient control samples should be collected.* This criterion was met. A control sample was collected from each dog prior to the application event.

16. *Samples should be stored in a manner that will minimize deterioration and loss of analytes between collection and analyses. Information of storage stability should be provided.* This criterion was partially met. The samples were stored frozen at the analytical laboratory; however, the storage conditions prior to receipt at the laboratory were not provided. Additionally, information regarding storage stability was not provided.

17. *Validated analytical methods of sufficient sensitivity are needed. Information on method efficiency (residue recovery) and limit of quantification (LOQ) should be provided.* These criteria were partially met. LOQ values for both permethrin and imidacloprid were provided. According to the Study Report, method validation studies were conducted for both chemicals, however, the complete method validation study and results were only provided for permethrin. Additionally, the Study Report did not distinguish between the recoveries of samples fortified prior to the analytical study (method validation samples) and during the analytical study (concurrent samples).

18. *Information on recovery samples must be included in the study report. A complete set of field recoveries should consist of at least one blank control sample and three or more each of a low-level and high-level fortification. These fortifications should be in the range of anticipated residue levels in the field study.* These criteria were not met. Field fortification samples were not utilized as part of this study.

19. *Raw residue data must be corrected if appropriate recovery values are less than 90 percent.* This criterion was not met. Samples were not corrected for recoveries. There were no field fortification samples collected and results for laboratory fortification samples were not clearly identified.

20. *Soil residues should be reported as mg or µg of pesticide active ingredient per body part sampled, if generated using the whole-body dosimetry techniques and on a surface area basis if the data were generated using the patch techniques (i.e., normalized on patch sample surface area; µg/cm^2 or mg/cm^2). Distributional data should be reported, to the extent possible.* This criterion does not apply. Residues were reported in mg/glove. The palmar surface area of the hands was not reported.

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Chemical: Permethrin

PC Code: 109701
HED File Code: 13000 Tox Reviews
Memo Date: 3/14/2006
File ID: DPD320041
Accession #: 412-06-0193

HED Records Reference Center
7/18/2006